PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

PHARMACIA & UPJOHN SPA
V.le Pasteur, 10
I-20014 Nerviano
ITALIE

Date of mailing (day/month/year) 19 September 2000 (19.09.00)	
Applicant's or agent's file reference FC 873/5	**IMPORTANT NOTIFICATION**
International application No. PCT/EP00/06545	International filing date (day/month/year) 10 July 2000 (10.07.00)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 19 July 1999 (19.07.99)
Applicant PHARMACIA & UPJOHN SPA et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An **asterisk(*)** appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The **letters "NR"** appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
19 July 1999 (19.07.99)	9916882.5	GB	15 Augu 2000 (15.08.00)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

Athina Nickitas-Etienne

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

To:
PHARMACIA & UPJOHN SPA
V. le Pasteur, 10
I-20014 Nerviano-Milan
ITALIE

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

Date of mailing (day/month/year) 25 January 2001 (25.01.01)	
Applicant's or agent's file reference FC 873/5	**IMPORTANT NOTICE**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/EP00/06545	10 July 2000 (10.07.00)	19 July 1999 (19.07.99)

Applicant
PHARMACIA & UPJOHN SPA et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,KP,KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CN,CR,CU,CZ,DE,DK,DM,EA,EE,EP,ES,FI,GB,GD,
   GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,MW,MX,
   NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   25 January 2001 (25.01.01) under No. WO 01/05382

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
J. Zahra

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Continuation of Form PCT/IB/308

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

Date of mailing (day/month/year)	IMPORTANT NOTICE
25 January 2001 (25.01.01)	
Applicant's or agent's file reference	**International application No.**
FC 873/5	PCT/EP00/06545

The applicant is hereby notified that, at the time of establishment of this Notice, the time limit under Rule 46.1 for making amendments under Article 19 has not yet expired and the International Bureau had received neither such amendments nor a declaration that the applicant does not wish to make amendments.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

CORRECTED VERSION

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 January 2001 (25.01.2001)

PCT

(10) International Publication Number
WO 01/05382 A1

(51) International Patent Classification[7]: A61K 31/70, A61P 35/00, A61K 31/505

(21) International Application Number: PCT/EP00/06545

(22) International Filing Date: 10 July 2000 (10.07.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9916882.5 19 July 1999 (19.07.1999) GB

(71) Applicant *(for all designated States except US)*: PHARMACIA & UPJOHN SPA [IT/IT]; Via Robert Koch, 1.2, I-20152 Milan (IT).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: GERONI, Maria, Cristina [IT/IT]; Via Correggio, 48, I-20149 Milan (IT). RIPAMONTI, Marina [IT/IT]; Vle Fulvio Testi, 91, I-20162 Milan (IT). CARUSO, Michele [IT/IT]; Via Desiderio, 3, I-20131 Milan (IT). SUARATO, Antonino [IT/IT]; Via Degli Imbriani, 39, I-20158 Milan (IT).

(81) Designated States *(national)*: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

(48) Date of publication of this corrected version:
12 April 2001

(15) Information about Correction:
see PCT Gazette No. 15/2001 of 12 April 2001, Section II

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/05382 A1

(54) Title: SYNERGISTIC COMPOSITION COMPRISING DAUNORUBICIN DERIVATIVES AND ANTIMETABOLITE COMPOUNDS

(57) Abstract: The combined use of 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyl daunorubicin or 4-demethoxy-N,N-bis(2-chloroethyl)-4'-methansulfonyl daunorubicin and an antimetabolite compound in the treatment of tumors, especially in the treatment or prevention of metastasis or in the treatment of tumors by the inhibition of angiogenesis.

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70) 14

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
FC 873		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/06545	10/07/2000	19/07/1999
International Patent Classification (IPC) or national classification and IPC A61K31/00		
Applicant PHARMACIA AND UPJOHN S.p.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
13/02/2001	02.05.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Langer, A Telephone No. +49 89 2399 7809

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/06545

I. Basis f th report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-5 as originally filed

Claims, No.:

1-11 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-4, 7, 9, 11 only partially in respect of novelty and inventive step.

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-4, 7, 9, 11 (incomplete search).

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-11 (with respect to searched subject-matter)
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-11 (with respect to searched subject-matter)
	No:	Claims	

Industrial applicability (IA) Yes: Claims 1-11
No: Claims

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

R it m III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Due to incomplete search of the subject-matter of **claims 1-4, 7, 9, 11** the opinion can only be established partially with regard to novelty and inventive step(see International Search Report).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following statement is based on an incomplete search (see item III and International Search Report).

1. Reference is made to the following documents:

   D1: US-A-4 853 221 (ELSLAGER EDWARD F ET AL) 1 August 1989 (1989-08-01)

   D2: WO 99 20264 A (DODD THOMAS J ;BIONUMERIK PHARMACEUTICALS INC (US); HAUSHEER FREDE) 29 April 1999 (1999-04-29)

2. The present application refers to antitumour compositions containing an alkylating anthracycline and an antimetabolite compound.

3. Document D1 discloses the use of antimetabolites for the treatment of tumours (claims).
   Document D2 discloses anti-neoplastic products containing for example daunorubicin, doxorubicin, epirubicin, idarubicin, 5-fluorouracil or gemcitabin (p. 40-43). The document further indicates that these substances are particularly suitable for combination chemotherapy (p. 63, line 20-26).

4. Nov_lty (Art. 33 (3) PCT)

The prior art does not disclose any products containing an alkylating anthracycline of formula Ia or Ib in combination with an antimetabolite. **Claims 1-11** therefore appear novel in terms of Art. 33 (3) PCT with respect to the searched subject-matter.

5. Inventive Step (Art. 33 (3) PCT)

Document D2, which is considered to represent the most relevant state of the art for **claim 1**, discloses anti-neoplastic products from which the subject-matter of claim 1 differs in that it contains a derivative of daunorubicin (formula Ia or Ib) in combination with an antimetabolite, while document D2 indicates the combined use of substances belonging to a group of more than 60 anti-neoplastic compounds, comprising daunorubicin and several antimetabolites such as 5-fluorouracil and gemcitabin.

The problem to be solved by the present invention may therefore be regarded as how to provide an alternative anti-neoplastic product. The solution proposed in claim 1 of the present application is considered as involving an inventive step with respect to the searched subject-matter for the following reasons:

The alkylating anthracyclines of formula Ia or Ib are described the prior art (p. 1 of the description) as providing the same advantages as in the present application. The skilled person would therefore regard it as a normal option to include this feature in the product described in document D2 in order to solve the problem posed. However, document D2 only refers to a combination of any of the compounds mentioned without specifying that one of it should be daunorubicin. Furthermore, even though suggesting the combination of the compounds in anti-neoplastic therapy in order to reduce the side effects, the document does not indicate the synergistic effect of the combination as observed with the product of the invention.

The same argumentation applies to **claims 2-11**.

6. Industrial applicability (Art. 33 (4) PCT)

For the assessment of the present claims 1-11 on the question whether they are

industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI

Certain documents cited

Certain published documents (Rule 70.10)

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO 00/50033	31/08/2000	31/01/2000	25/02/1999
WO 00/66093	09/11/2000	04/04/2000	29/04/1999

Although the above mentioned document WO 00/66093 is not prior art according to R. 64.1(a) PCT, it discloses the subject-matter of **claims 1, 3-11** (claims). The document may therefore in some contracting states be relevant for the evaluation of the present application.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
FC 873/5		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/ 06545	10/07/2000	19/07/1999
Applicant		
PHARMACIA AND UPJOHN S.P.A.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   SYNERGISTIC COMPOSITION COMPRISING DAUNORUBICIN DERIVATIVES AND ANTIMETABOLITE COMPOUNDS

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1

   [X] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/[redacted]00/06545

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/70 A61P35/00 A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4 853 221 A (ELSLAGER EDWARD F ET AL) 1 August 1989 (1989-08-01) abstract; claim 1; tables 6,7 ---	1-11
X	WO 99 20264 A (DODD THOMAS J ;BIONUMERIK PHARMACEUTICALS INC (US); HAUSHEER FREDE) 29 April 1999 (1999-04-29) page 17 -page 19 page 40 page 41 page 43	1-11
Y	page 63, line 20-25; claims 16,17 ---	1-11
E	WO 00 50033 A (CARUSO MICHELE ;GERONI CRISTINA (IT); PHARMACIA & UPJOHN SPA (IT);) 31 August 2000 (2000-08-31) abstract; claim 1 --- -/--	1-11

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 December 2000	03/01/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gonzalez Ramon, N

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/[redacted]00/06545

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
E	WO 00 50032 A (CARUSO MICHELE ;GERONI CRISTINA (IT); PHARMACIA & UPJOHN SPA (IT);) 31 August 2000 (2000-08-31) abstract; claim 1	1-11
E	WO 00 66093 A (GERONI MARIA CRISTINA ;CARUSO MICHELE (IT); PHARMACIA & UPJOHN SPA) 9 November 2000 (2000-11-09) claims 3,11,25,35	1-11
X,P	WO 99 48503 A (CARUSO MICHELE ;GERONI CRISTINA (IT); PHARMACIA & UPJOHN SPA (IT);) 30 September 1999 (1999-09-30) abstract; claim 1	1-11

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No
PCT 00/06545

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4853221 A	01-08-1989	US 4391809 A	05-07-1983
WO 9920264 A	29-04-1999	US 5919816 A	06-07-1999
		AU 1090899 A	10-05-1999
		CN 1276720 T	13-12-2000
		EP 1033981 A	13-09-2000
		US 6066645 A	23-05-2000
		US 6066668 A	23-05-2000
		US 6040304 A	21-03-2000
		US 6046159 A	04-04-2000
		US 6048849 A	11-04-2000
		US 6046234 A	04-04-2000
		US 6057361 A	02-05-2000
		US 6040312 A	21-03-2000
		US 6043249 A	28-03-2000
		US 6040294 A	21-03-2000
		US 6025488 A	15-02-2000
WO 0050033 A	31-08-2000	AU 2668100 A	14-09-2000
WO 0050032 A	31-08-2000	AU 2545900 A	14-09-2000
WO 0066093 A	09-11-2000	NONE	
WO 9948503 A	30-09-1999	AU 3331499 A	18-10-1999
		BR 9908391 A	31-10-2000
		NO 20004703 A	20-09-2000

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-4,7,9,11

Present claims 1,2,7,9,11 relate to a product/compound defined by reference to a desirable characteristic or property, namely "antimetabolite compound"
The claims cover all products/compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such products/compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product/compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the products/compounds specifically mentioned in the description page 2, the example and in claims 5,6,8,10.

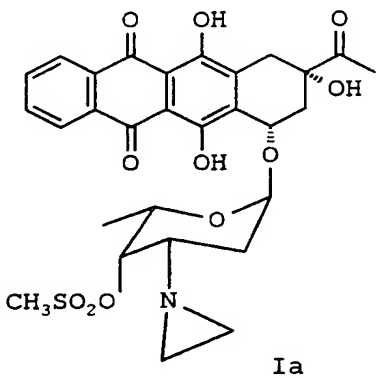
The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

SYNERGISTIC COMPOSITION COMPRISING DAUNORUBICIN DERIVATIVES AND ANTIMETABOLITE COMPOUNDS

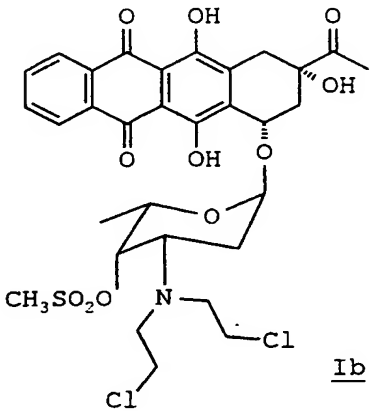
The present invention relates in general to the field of cancer treatment and, more particularly, provides an antitumor composition comprising an alkylating anthracycline and an antimetabolite compound, having a synergistic or additive antineoplastic effect.

The present invention provides, in a first aspect, a pharmaceutical composition for use in antineoplastic therapy in mammals, including humans, comprising

- an alkylating anthracycline of formula Ia or Ib :



Ia



Ib

- an antimetabolite compound, and a pharmaceutically acceptable carrier or excipient.

The chemical names of the alkylating anthracyclines of formula Ia and Ib are 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyl daunorubicin (Ia) and 4-demethoxy-N,N-bis(2-chloroethyl)-4'-methansulfonyl daunorubicin (Ib). These alkylating anthracyclines were described in Anticancer Drug Design (1995), vol. 10, 641-653, and claimed respectively in US-A-5,532,218 and US-A-5,496,800. Both compounds intercalate into DNA via the chromophore and alkylate guanine at N^7 position in DNA major groove via their reactive moiety on position 3' of the amino sugar. Compounds Ia and Ib are able to circumvent the resistance to all major classes of

cytotoxics, indicating that the compounds represent a new class of cytotoxic antitumor drugs.

Antimetabolites are described in various scientific publications. The main representatives of this wide class of drugs are: the antifolates such as methotrexate, raltitrexed and trimetrexate; the 5-fluoropyrimidine compounds such as 5-fluorouracil, floxuridine and capecitabine; the cytidine analogs like cytarabine, azacitidine and gemcitabine. See for example the review: Cancer, Principles and Practice of Oncology, Lippincott-Raven Ed. (1997), 432-452. The 5-fluoropyrimidine compounds and the cytidine analogs are the preferred antimetabolite compounds to be used in the present invention, more preferably 5-fluorouracil or gemcitabine. The present invention also provides a product comprising an alkylating anthracycline of formula Ia or Ib as defined above and an antimetabolite compound, as combined preparation for simultaneous, separate or sequential use in antitumor therapy.

A further aspect of the present invention is to provide a method of treating a mammal including humans, suffering from a neoplastic disease state comprising administering to said mammal an alkylating anthracycline of formula Ia or Ib as defined above and an antimetabolite compound, in amounts effective to produce a synergistic antineoplastic effect.

The present invention also provides a method for lowering the side effects caused by antineoplastic therapy with an antineoplastic agent in mammals, including humans, in need thereof, the method comprising administering to said mammal a combination preparation comprising an antimetabolite compound as defined above and an alkylating anthracycline of formula Ia or Ib, as defined above, in amounts effective to produce a synergistic antineoplastic effect.

By the term "a synergistic antineoplastic effect" as used herein is meant the inhibition of the growth tumor,

preferably the complete regression of the tumor, administering an effective amount of the combination of an alkylating anthracycline of formula Ia or Ib as defined above and a antimetabolite compound to mammals, including human.

By the term "administered " or "administering" as used herein is meant parenteral and /or oral administration. By "parenteral" is meant intravenous, subcutaneus and intramuscolar administration. In the method of the subject invention, the alkylating anthracycline may be administered simultaneously with the compound with the antimetabolite compound activity, for example of the 5-fluoropyrimidine or cytidine class, or the compounds may be administered sequentially, in either order. It will be appreciated that the actual preferred method and order of administration will vary according to, inter alia, the particular formulation of the alkylating anthracycline of formula Ia or Ib being utilized, the particular formulation of the antimetabolite compound, such as one of the 5-fluoropyrimidine or cytidine class, being utilized, the particular tumor model being treated, and the particular host being treated.

In the method of the subject invention, for the administration of the alkylating anthracycline of formula Ia or Ib, the course of therapy generally employed is from about 0.1 to about 200 mg/m^2 of body surface area. More preferably, the course therapy employed is from about 1 to about 50 mg/m^2 of body surface area.

In the method of the subject invention, for the administration of the antimetabolite compound the course of therapy generally employed is from about 0.1 to about 10 g/m^2 of body surface area. More preferably, the course therapy employed is from about 1 mg/m^2 to about 5 g/m^2 of body surface area. The antineoplastic therapy of the present invention is in particular suitable for treating breast, ovary lung,

colon, kidney, stomach, pancreas, liver, melanoma, leukemia and brain tumors in mammals, including humans.

In a further aspect, the present invention is directed to the preparation of a pharmaceutical composition containing an effective amount of an alkylating anthracycline of formula Ia or Ib as defined above and an antimetabolite compound in the prevention or treatment of metastasis or for the treatment of tumors by angiogenesis inhibition, as well as to the use of an alkylating anthracycline of formula Ia or Ib as defined above and an antimetabolite compound for the treatment of tumors by angiogenesis inhibition or for the treatment or prevention of metastasis.

As stated above, the effect of an alkylating anthracycline of formula Ia or Ib and an antimetabolite compound, such as a 5-fluoropyrimidine or cytidine derivative, is significantly increased without a parallel increased toxicity. In other words, the combined therapy of the present invention enhances the antitumoral effects of the alkylating anthracycline and of the antimetabolites and thus yields the most effective and least toxic treatment for tumors.

The superadditive actions of the combination preparation of the present invention may be shown for instance by in vivo tests for the antileukemic activity on disseminated L1210 murine leukemia. The combination of Ia with gemcitabine (Table 1) or 5-Fluorouracil tested at the different doses and schedules, produces favorable ILS% values (Increase in life span: [(median survival time of treated mice/median survival time of controls)x 100]-100), indicating a synergistic effect.

Table 1 shows the antileukemic activity on disseminated L1210 murine leukemia obtained by combining the above PNU 159548 derivative with gemcitabine.

At the dose of 15 and 60 mg/kg of gemcitabine alone (ip day 1 after tumor injection) and at the dose of 1 and 1.5 mg/kg of PNU 159548 alone (iv day 1 after tumor injection, administered 2h after gemcitabine) were associated, without toxicity, with ILS% values of 50 and 83 and 33 and 67, respectively. By combining gemcitabine and PNU 159548 at the same doses and with the same schedule, an increase of activity with ILS% values of 117 and 204 were observed, indicating a synergistic effect as shown by the combination index (CI) of 1.4 and 1.3, respectively.

Table 1: Antileukemic activity against disseminated L1210[1] murine leukemia of PNU-159548 (I) in combination with gemcitabine

Compound	Treatment schedule	Dose (mg/kg/day)	ILS%[2]	LTS[3]	TOX[4]	CI[5]
PNU 159548	iv +1(*)	1 1.5	33 67	0/10 0/20	0/10 0/20	NA NA
Gemcitabine	ip +1	15 60	50 83	0/10 0/20	0/10 0/20	NA NA
PNU 159548 + gemcitabine	iv +1(*) ip +1	1 + 15 1.5 + 60	117 204	0/10 4/20	0/10 2/20	1.4 1.3

1. L1210 leukemia cells (10^5/mouse CD2F1) are injected IV on Day 0.
2. Increase in life span: [(median survival time of treated mice/median survival time of controls) x 100] -100.
3. LTS: long-term survivors (>60 days) at the end of the experiments
4. Number of toxic deaths/number of mice.
5. C.I. = combination Index : <1 antagonistic; 1 additive; >1 synergistic

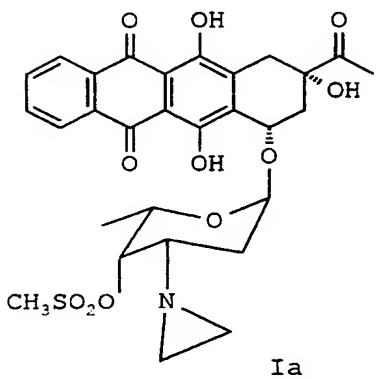
(*)administered 2h after gemcitabine

NA: not applicable

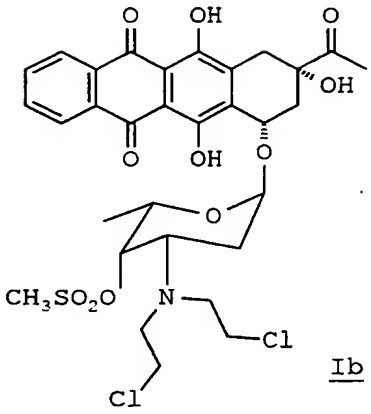
For these experiments Ia was solubilized in [Cremophor® /EtOH = 6.5:3.5]/[normal saline]=20/80 v/v, while standard pharmaceutical preparation were used for the antimetabolite compounds.

Claims

1. A product containing an alkylating anthracycline of formula Ia or Ib:



Ia



Ib

and an antimetabolite compound as a combined preparation for simultaneous, separate or sequential use in the treatment of tumors.

2. A product according to claim 1 wherein the alkylating anthracycline is 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methanesulfonyl daunorubicin.

3. A product according to claim 1 or 2 wherein the antimetabolite compound is a cytidine analog.

4. A product according to claim 1 or 2 wherein the antimetabolite compound is a 5-fluoropyrimidine.

5. A product according to claim 3 wherein the cytidine analog is gemcitabine.

6. A product according to claim 4 wherein the 5-fluoropyrimidine is 5-fluorouracil.

7. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient and, as active ingredient, an alkylating anthracycline of formula Ia or Ib as defined in claim 1 and an antimetabolite compound.

8. A composition according to claim 7 wherein the antimetabolite compound is 5-fluorouracil or gemcitabine.

9. Use of an alkylating anthracycline of formula Ia or Ib as defined in claim 1 and an antimetabolite compound in the preparation of a medicament for use in the treatment of tumors.

10. Use according to claim 8 wherein the antimetabolite compound is 5-fluorouracil or gemcitabine.

11. Use of an alkylating anthracycline of formula Ia or Ib as defined in claim 1 and an antimetabolite compound in the preparation of a medicament for use in the prevention or treatment of metastasis or in the treatment of tumors by inhibition of angiogenesis.

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

MAZZINI, Giuseppe
PHARMACIA & UPJOHN S.P.A.
Viale Pasteur, 10
I-20014 Nerviano (Milano)
ITALIE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	02.05.2001
Applicant's or agent's file reference FC 873	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/06545	10/07/2000	19/07/1999

Applicant
PHARMACIA AND UPJOHN S.p.A. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Exner, K Tel.+49 89 2399-7826

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
FC 873		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/06545	10/07/2000	19/07/1999
International Patent Classification (IPC) or national classification and IPC A61K31/00		
Applicant PHARMACIA AND UPJOHN S.p.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
13/02/2001	02.05.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Langer, A Telephone No. +49 89 2399 7809

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/06545

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-5 as originally filed

Claims, No.:

1-11 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-4, 7, 9, 11 only partially in respect of novelty and inventive step.

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-4, 7, 9, 11 (incomplete search).

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-11 (with respect to searched subject-matter)
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-11 (with respect to searched subject-matter)
	No:	Claims	

Industrial applicability (IA) Yes: Claims 1-11
No: Claims

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Re item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Due to incomplete search of the subject-matter of **claims 1-4, 7, 9, 11** the opinion can only be established partially with regard to novelty and inventive step(see International Search Report).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following statement is based on an incomplete search (see item III and International Search Report).

1. Reference is made to the following documents:

   D1: US-A-4 853 221 (ELSLAGER EDWARD F ET AL) 1 August 1989 (1989-08-01)

   D2: WO 99 20264 A (DODD THOMAS J ;BIONUMERIK PHARMACEUTICALS INC (US); HAUSHEER FREDE) 29 April 1999 (1999-04-29)

2. The present application refers to antitumour compositions containing an alkylating anthracycline and an antimetabolite compound.

3. Document D1 discloses the use of antimetabolites for the treatment of tumours (claims).
   Document D2 discloses anti-neoplastic products containing for example daunorubicin, doxorubicin, epirubicin, idarubicin, 5-fluorouracil or gemcitabin (p. 40-43). The document further indicates that these substances are particularly suitable for combination chemotherapy (p. 63, line 20-26).

4. Novelty (Art. 33 (3) PCT)

The prior art does not disclose any products containing an alkylating anthracycline of formula Ia or Ib in combination with an antimetabolite. **Claims 1-11** therefore appear novel in terms of Art. 33 (3) PCT with respect to the searched subject-matter.

5. Inventive Step (Art. 33 (3) PCT)

Document D2, which is considered to represent the most relevant state of the art for **claim 1**, discloses anti-neoplastic products from which the subject-matter of claim 1 differs in that it contains a derivative of daunorubicin (formula Ia or Ib) in combination with an antimetabolite, while document D2 indicates the combined use of substances belonging to a group of more than 60 anti-neoplastic compounds, comprising daunorubicin and several antimetabolites such as 5-fluorouracil and gemcitabin.
The problem to be solved by the present invention may therefore be regarded as how to provide an alternative anti-neoplastic product. The solution proposed in claim 1 of the present application is considered as involving an inventive step with respect to the searched subject-matter for the following reasons:
The alkylating anthracyclines of formula Ia or Ib are described the prior art (p. 1 of the description) as providing the same advantages as in the present application. The skilled person would therefore regard it as a normal option to include this feature in the product described in document D2 in order to solve the problem posed. However, document D2 only refers to a combination of any of the compounds mentioned without specifying that one of it should be daunorubicin. Furthermore, even though suggesting the combination of the compounds in anti-neoplastic therapy in order to reduce the side effects, the document does not indicate the synergistic effect of the combination as observed with the product of the invention.
The same argumentation applies to **claims 2-11**.

6. Industrial applicability (Art. 33 (4) PCT)

For the assessment of the present claims 1-11 on the question whether they are

industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI

Certain documents cited

Certain published documents (Rule 70.10)

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO 00/50033	31/08/2000	31/01/2000	25/02/1999
WO 00/66093	09/11/2000	04/04/2000	29/04/1999

Although the above mentioned document WO 00/66093 is not prior art according to R. 64.1(a) PCT, it discloses the subject-matter of **claims 1, 3-11** (claims). The document may therefore in some contracting states be relevant for the evaluation of the present application.